UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,311	10/31/2003	James McSwiggen	MBHB04-372 (400/137)	9826

20306 7590 06/28/2006

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,311	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,16,17,21,23,24,30 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,16,17,21,23,24,30 and 33* is/are rejected.

7)☒ Claim(s) *37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application/Amendments

Applicant's response filed 4/27/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/24/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 4/27/2006, claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are pending in the application and currently under examination.

Information Disclosure Statement

As explained in the previous Action, the information disclosure statement filed June 8, 2005 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as it pertains to JP08208687, which is in Japanese.

Sequences

In the previous Action, acknowledgement was made of Applicants' request for entry of a new sequence listing, which adds SEQ ID NO:311 to the application. Applicants stated that SEQ

ID NO:311 corresponds to GenBank entry NM_000345 (which the Examiner notes is cited in the instant application as originally filed) and that sequence SEQ ID NO:311 first appeared in GenBank on Feb. 6, 2001. The new sequence listing was added in full.

Response to Arguments—Priority

The previous office action stated that support for pending claims to double-stranded siNA molecules targeting SEQ ID NO:311, corresponding to a synuclein-1 (SNCA) gene, represented by GenBank Accession No. NM_000345, could not be found in provisional application 60/363,124, filed March 11, 2002, to which priority was claimed.

In response, Applicants have amended independent claim 37 to recite "siRNA" and have pointed out with particularity where support for claim 37 may be found in provisional application 60/363,124 (see Applicants' remarks of 4/27/06, pp. 5-9). On this basis, Applicants now assert that the currently pending claims all find support in provisional application 60/363,124, filed March 11, 2002.

Applicants remarks have been fully considered and are found persuasive.

In light of Applicants' amendments and remarks, showing where adequate written description support may be found, Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are considered by the Examiner to have adequate written description support in provisional application 60/363,124, filed March 11, 2002. Specifically, adequate written description support for claims to a double stranded, chemically modified siRNA complementary to SEQ ID NO:311, does exist in 60/363,124.

For these reasons, Applicants' priority date for the currently claimed invention is considered to be that of provisional application 60/363,124, March 11, 2002.

Response to Arguments—Double Patenting

Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 15, 16, 17, 18, 21, 30, and 31 of copending Application No. 10/861,060, as amended on 1/23/06, in view of Higuchi et al. (1998) *Experimental Neurology* 153:164-166.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim the same or similar subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Both the instant application and the conflicting application have been amended, necessitating the new grounds of rejection stated herein; namely, the application of Higuchi et al. as a secondary reference.

An updated review of copending Application No. 10/861,060, shows that the application was amended on 1/23/06 and that the application now claims a chemically synthesized, and chemically modified, double-stranded short (18 to about 27 nucleotides) nucleic acid molecule that is complementary to a mutant human SNCA nucleotide sequence. Also claimed are nucleic acid molecules thereof having 2'-deoxy, 2'-fluoro modified sugars, phosphorothioate linkages, and terminal cap moieties, identical to those recited in the instant application.

Higuchi et al. teach that mutations in α-synuclein may predispose persons to familial Parkinson's disease, and teach that α-synuclein, in general, plays a pivotal role in neurological disorders such as Alzheimer's disease (page 164). Higuchi et al. state that the Ala53Thr mutation in α-synuclein is likely to be responsible only for a rare autosomal dominant form of PD (page 165).

Accordingly, one of ordinary skill in the art would immediately recognize that the invention now claimed in the instant application (10/698,311) is obvious over the inventions claimed in copending application 10/861,060. Mutant forms of SNCA were known at the time of filing to be associated with certain forms of neurological disease and one of skill in the art would have been motivated and have had a reasonable expectation of success in targeting such forms for inhibition using double stranded interfering RNAs, as now claimed.

Applicants arguments and/or reply:

The reply of 4/27/06 states that Applicants will consider submitting a terminal disclaimer upon indication of allowable claims.

No claims are allowable at this time.

No Arguments Presented—Claim Objections

Pursuant to MPEP §608.01(m), Claim 37 stands objected to because it contains several periods. According to MPEP 608.01(m) each claim should end with a period, but periods should not be used elsewhere except in abbreviations. Appropriate correction is required.

Applicants have not addressed this objection in their remarks filed 4/27/06

The reply of 4/27/06 does not comply with 37 CFR §1.111(b) because the reply does not address every ground of objection and rejection made in the prior Office action. This may be an inadvertent omission. The reply as whole has been accepted as a bona fide attempt to advance prosecution.

Response to Arguments—Claim Rejections - 35 USC § 103

Claims 3, 21, 23, 24, 30, 33, and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (US 2004/0259247), Driscoll et al. (WO 01/49844), GenBank Accession No. D31839 gene sequence, published by NCBI on Feb. 7, 1995, and Parrish et al. (2000) *Molecular Cell* 6:1077-1087 (cited in Applicants' IDS of 8/6/04).

The Examiner notes that claim 37 as amended now recites a double stranded short interfering RNA comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides complementary to human synuclein RNA, SEQ ID NO:311.

Applicants' arguments addressed:

Applicants argue that the cited references, taken individually or in combination, do not render the claimed invention obvious. Applicants argue that the cited references provide no motivation to make the instant invention. Applicants argue that Tuschl et al. teach away from the instantly claimed invention and/or provide no motivation to make siRNA comprising 2'-fluoro modifications, as now recited in the amended claims, in as much as Tuschl et al. teach that extensive 2'-deoxy and 2'-O-methyl modifications abolish siRNA activity (Remarks, page 12). Applicants argue that the cited references provide no reasonable expectation of success for making the claimed invention (Remarks, page 13).

Applicants' remarks have been fully considered but are not found persuasive.

Tuschl et al. do not teach away from the invention as now claimed. While, Tuschl et al. teach that extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl will abolish RNAi activity, Tuschl et al. do not teach that modification with 2'-fluoro will abolish RNAi activity. Furthermore, the instant claims are not directed 2'-deoxy (2'-H) or 2'-O-methyl modifications.

In fact, paragraphs 14, 15 and 16, page 2, of Tuschl et al. explicitly teach that double stranded RNA molecules may be modified in order to increase their resistance to nuclease degradation; that replacement of the 2'-OH significantly enhances the nuclease resistance of the siRNA overhang in culture medium; that in preferred sugar modified ribonucleotides, the 2'-OH group is replaced by a fluorine (F). A review of Tuschl et al. fails to find any disclosure specifically teaching away from 2'-deoxy-2'-fluoro modified siRNAs.

Additionally, Parrish et al., a reference introduced in view of Applicants' amendments, as further evidence that 2'-fluoro modifications were known to be tolerated in dsRNAs used for RNAi-mediated gene expression inhibition. Parrish et al. state that "Modification of uracil with

2'-fluorouracil was compatible with RNAi activity..." (page 1081; Fig. 5), and that "modification of at least 1/4 of bases to a 2' fluoro group (which preserves A form structure [...]) were compatible function as an RNAi trigger" (page 1084)

Although, the Parrish et al. reference is directed to long dsRNAs for RNAi in worms, it is clear from Parrish et al. and Tuschl et al. that, at the time the instant invention was made, one of skill in the RNAi field would have recognized the potential benefits and utility of making 2'-fluoro modifications in double stranded, interfering RNAs.

Thus, neither Tuschl et al. nor Parrish et al. teach away from the claimed invention.

The references as a whole provide ample motivation and reasonable expectation of success to make and use the claimed invention.

As explained in the previous Action, Driscoll et al. provide explicit teachings, suggesting and demonstrating the use of double stranded, interfering RNA molecules to inhibit the expression of human α-synuclein to treat or inhibit the progression of Parkinson's disease. More specifically, Driscoll et al. teach inverted repeat (IR) constructs expressing interfering, double stranded, hairpin RNA complementary to nucleic acid sequence GenBank Acc. No. D31839, encoding a human alpha-synuclein protein (page 45, lines 32-34), which sequence is present in SEQ ID NO: 311.

Furthermore, while Driscoll et al. teach that the sense and antisense coding sequences of their IR construct may be as short as 20 nucleotides (page 11), Tuschl et al. teach that using short interfering dsRNA in human cells confers a distinct advantage or beneficial result in that it induces potent, target specific silencing without activating the interferon response pathway (paragraphs 34, 137, 149,150).

Thus, it would have been obvious to one of ordinary skill in the art to use the cDNA sequence of GenBank Accession No. D31839 as suggested by Driscoll et al. to generate short interfering RNA sequences, comprising 2'-fluoro modifications as taught by both Tuschl et al. and Parrish et al., for inhibition of the human alpha-synuclein sequence represented by SEQ ID NO:311.

Finally, one would have a reasonable expectation of success given that Tuschl et al. provide detailed guidelines and rules for generating 2'-modified siRNAs, including 2'-fluoro modified siRNAs, to any known gene, and that methods of RNA synthesis are known in the art, and given that gene sequence for human alpha-synuclein was known and its potential therapeutic significance as a target for gene therapy was well established.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

*****

Claims 16 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (US 2004/0259247), Driscoll et al. (WO 01/49844), GenBank Accession No. D31839 gene sequence, published by NCBI on Feb. 7, 1995, and Parrish et al., as applied to the claims above, and further in view of U.S. Patent 5,998,203 to Matulic-Adamic (1999) and Ortigao et al. (1992) *Antisense Res. Dev.* 2:129-146.

Applicants have not specifically addressed this rejection in their remarks filed 4/27/06

The reply of 4/27/06 does not comply with 37 CFR §1.111(b) because the reply does not address every ground of objection and rejection made in the prior Office action. Specifically, the reply fails to address the rejection of claims 16 and 17 over Tuschl et al., Driscoll et al., GenBank Accession No. D31839, in view of U.S. Patent 5,998,203 to Matulic-Adamic (1999) and Ortigao et al. (1992) *Antisense Res. Dev.* 2:129-146.

Thus, the instant claims stand rejected for lack of obviousness, for reasons of record as well as for the reasons given above. Additionally, claims 16 and 17 now stand rejected over Parrish et al., in view of the amendment to claim 37, for the reasons given above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Louis Wollenberger
Examiner, Art Unit 1635
June 12, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER